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PAPER

No evidence that severity of stroke in internal carotid occlusion is related to collateral arteries

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Background/Aim: The neurological effects of internal carotid artery (ICA) occlusion vary between patients. The authors investigated whether the severity of symptoms in a large group of patients with ipsilateral or/and contralateral ICA occlusion at presentation with ocular or cerebral ischaemic symptoms could be explained by patency of other extra or intracranial arteries to act as collateral pathways.
Methods: The authors prospectively identified all patients (n = 2881) with stroke, cerebral transient ischaemic attack (TIA), retinal artery occlusion (RAO), and amaurosis fugax (AFx) presenting to our hospital over five years, obtained detailed history and examination, and examined the intra and extracranial arteries with carotid and colour-power transcranial Doppler ultrasound. For this analysis, all those with intracranial haemorrhage on brain imaging and cerebral events without brain imaging were excluded.
Results: Among 2228/2397 patients with brain imaging (1713 ischaemic strokes, 401 cerebral TIAs, 193 AFx, and 90 RAO) who underwent carotid Doppler, 195 (9%) had ICA occlusion. Among those patients with cortical events, disease in potential collateral arteries (contralateral ICA, external carotid, ipsilateral or contralateral vertebral or intracranial arteries) was equally distributed among patients with severe and mild ischaemic presenting symptoms.
Conclusion: The authors found no evidence that the clinical presentation associated with an ICA occlusion was related to patency of other extra or intracranial arteries to act as collateral pathways. Further work is required to investigate what determines the clinical effects of ICA occlusion.

People who occlude their internal carotid artery (ICA) may do so asymptomatically, or may experience neurological effects ranging from transient ischaemic attack (TIA) to major disabling stroke.[1] The reason for such variation is uncertain, but one possible explanation is that severe strokes occur in patients whose potential collateral pathways were poor because of disease in, or developmental absence of, other extra or intracranial arteries supplying the brain.

Although there are several studies on ICA occlusion and type of symptoms, few have tried to determine why some patients present with severe symptoms and others do not. The few previous studies that do relate symptoms to intracranial flow were small,[2–5] or only included TIA or minor stroke, not all stroke severities.[2–4] Two[3 5] found an association between symptoms and collateral flow in mild stroke and two did not.[2 4]

Other studies were biased because they only included dead patients[6] or those undergoing angiography.[7 8] One study related the extent of cerebral infarction on brain imaging (but not symptoms) to collateral flow.[9] Some studies investigated the risk of recurrent stroke in longstanding ICA occlusion.[10–12] One of these studies found that recurrent stroke distal to a symptomatic ICA occlusion was associated with *increased* volume flow in collaterals (contralateral ICA), counterintuitive to the hypothesis that better collateral flow is protective.[11] Previous studies mainly examined intracranial collateral pathways[2–10] and only two looked at collateral potential in the extracranial arteries.[11 12]

The failure of previous studies to find any consistent association between collaterals and symptoms may be because they generally included patients with only mild symptoms. Therefore, our aim was to explore the influence of the collateral pathways on the nature and severity of symptoms in a large, consecutive, hospital based series of patients presenting with ICA occlusion and new cerebral or ocular ischaemic symptoms. We hypothesised that patients with ICA occlusion at presentation with severe stroke symptoms were more likely to have disease in other extra or intracranial arteries, impairing their function as collaterals.

METHODS

From November 1994 to April 1999, we prospectively identified all patients (including first and recurrent events) presenting to our stroke service with acute stroke, cerebral transient ischaemic attack (TIA), amaurosis fugax (AFx), and retinal artery occlusion (RAO). We recorded whether there was a history of prior stroke or TIA.

A stroke physician examined the patient as soon as possible following onset of symptoms. Those with acute stroke were classified clinically according to the Oxfordshire Community Stroke Project (OCSP).[13] Cerebral TIAs were categorised as posterior circulation or anterior circulation, then the anterior circulation TIAs were further divided into lacunar or cortical TIAs according to the presence or absence of cortical symptoms. RAO was defined as monocular visual loss, partial or complete, lasting more than 24 hours likely to be due to vascular disease of the retina. Brain imaging (CT or

Abbreviations: ACA, anterior cerebral artery; ACoA, anterior communicating artery; AFx, amaurosis fugax; CCA, common carotid artery; ECA, external carotid artery; ICA, internal carotid artery; LACI, lacunar infarct; MCA, middle cerebral artery; OCSP, Oxfordshire Community Stroke Project; PACI, partial anterior circulation infarct; PCoA, posterior communication artery; POCI, posterior circulation infarct; RAO, retinal artery occlusion; TACI, total anterior circulation infarct; TIA, transient ischaemic attack.

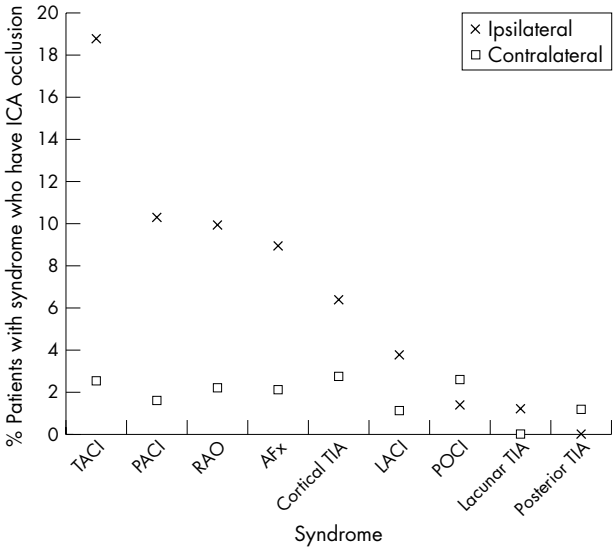

Figure 1 Proportion of patients with ipsilateral or contralateral ICA occlusion by type of presentation with cerebral or retinal ischaemic syndromes.

MRI) was done in patients with acute stroke, and when clinically indicated in patients with cerebral TIA, RAO, and AFx (for example, in patients with multiple or atypical attacks) immediately after medical assessment, in order to identify those with intracranial haemorrhage and stroke ''mimics''. We classified infarct site and size using a validated stroke imaging scoring system.[14 15]

Patients underwent carotid colour Doppler ultrasound imaging (Acuson 128XP 10V, 7 MHz multifrequency probe (Siemens, Germany)) by a consultant neuroradiologist or an experienced neuroradiographer, blinded, where possible, to the type and the side of clinical symptoms immediately after medical assessment. Presence and severity of stenosis in both ICAs, external carotid arteries (ECAs), and common carotid arteries (CCAs) were measured using velocity criteria and lesion appearance.[16] Complete ICA occlusion was diagnosed if there was no colour flow in the lumen of the vessel and no detectable Doppler signal. Flow direction (orthograde or retrograde) and velocity in the vertebral arteries was also recorded. Occluded vertebral arteries were diagnosed when a clear view of the vertebral canal was obtained but no flow was detected.

The intracranial vessels: A1 segment of the anterior cerebral artery (ACA), anterior communicating artery (ACoA), posterior communicating artery (PCoA), middle cerebral artery (MCA), P1 and P2 segments of posterior cerebral artery, ophthalmic artery, intracranial portion of the ICAs and basilar artery, were examined using colour power transcranial Doppler by the same ultrasonographer at the time of carotid imaging, in as many patients as possible. A 2 MHz probe was used for the trans-temporal and suboccipital approaches and a 7 MHz for the transorbital approach. The ultrasonographer made a diagnosis of ''normal'', ''reduced but still detectable flow'', ''occlusion'', ''hyperaemia'', or ''focal stenosis'' using previously reported criteria.[17]

For patients with cortical brain events (that is, total anterior circulation infarcts, TACIs, partial anterior circulation infarcts, PACIs, and cortical TIAs) and an ipsilateral ICA occlusion, we compared the severity of the clinical syndrome with disease in the other extracranial arteries or patterns of flow in the intracranial circulation. We also sought any association between prior TIA or stroke and the severity of current symptoms using χ^2 tests or χ^2 tests for trend. We performed these analyses in two different ways: firstly, we included those patients with no brain imaging; and then we repeated the analyses after excluding patients with cerebral symptoms (that is, stroke and cortical TIA) and no brain imaging. Here we report results after the exclusion of patients with cerebral symptoms and no brain imaging.

RESULTS

Patients

Between November 1994 to April 1999, 2881 patients with stroke, cerebral TIA, RAO, or AFx were identified, of whom 2292 had CT or MR brain imaging (96% of strokes and 61% of cerebral TIAs). 148 with intracerebral haemorrhage and 336 patients with cerebral symptoms and no brain imaging were excluded. Of the remaining 2397 patients, there were 1713 ischaemic strokes, 401 cerebral TIAs, 193 AFx, and 90 RAO.

Of 2228 patients (93%) with carotid Doppler imaging, 195 (9%) had ICA occlusions (fig 1). Of the 195 patients with ICA occlusions, 146 (75%) had an occlusion ipsilateral to the brain or eye lesion only, 36 (18%) had a contralateral occlusion only, eight had bilateral occlusions; and a further

Table 1 Disease of the contralateral internal carotid artery, ipsilateral or contralateral external carotid arteries, and vertebral arteries in patients with cortical symptoms and an ipsilateral ICA occlusion

	TACI and ipsilateral ICA occlusion (n = 22)	PACI and ipsilateral ICA occlusion (n = 70)	Cortical TIA and ipsilateral ICA occlusion (n = 14)	Other patients with any ICA occlusion (n = 89)
Contralateral ICA disease ⩾70% stenosis, n (%)	5 (23%)	20 (29%)	5 (36%)	47 (53%)
Any ipsilateral ECA stenosis, n (%)	10 (45%)	29 (41%)	5 (36%)	42 (47%)
Any contralateral ECA stenosis, n (%)	7 (32%)	18 (26%)	4 (29%)	36 (40%)
Ipsilateral vertebral artery occluded or reduced flow, n (%)	1 (5%)	8 (11%)	0 (0%)	2 (2%)
Contralateral vertebral artery occluded or reduced flow, n (%)	1 (5%)	7 (10%)	0 (0%)	2 (2%)

ICA, internal carotid artery; ECA, external carotid artery.
Ipsilateral vertebral artery is on the same side of the neck as the ipsilateral ICA.
''Other'' includes the contralateral occlusions, and the RAO, AFx, LACI, lacunar TIA, POCI, and posterior circulation TIA with ipsilateral occlusions.

Table 2 Transcranial Doppler data from patients with an ipsilateral internal carotid artery occlusion, divided according to presenting syndromes

Artery		TACI and ipsilateral ICA occlusion (n = 22)	PACI and ipsilateral ICA occlusion (n = 70)	Cortical TIA and ipsilateral ICA occlusion (n = 14)	Other patients with any ICA occlusion (n = 89)
Number of patients in whom TCD was attempted		19	57	12	74
Ipsilateral bone window adequate		16	30	8	50
Basilar artery	Reduced flow	0 (0%)	2 (7%)	0 (0%)	3 (6%)
	Invisible	7 (44%)	15 (50%)	2 (25%)	21 (42%)
	Normal	9 (56%)	13 (43%)	6 (75%)	26 (52%)
Ipsilateral ACA (A1 direction)	Correct	2 (13%)	3 (10%)	1 (12%)	18 (36%)
	Reversed	8 (50%)	12 (40%)	4 (50%)	10 (20%)
	Invisible	6 (32%)	15 (50%)	3 (38%)	22 (44%)
Ipsilateral MCA	Abnormal	13 (81%)	23 (77%)	4 (50%)	17 (34%)
	Normal	3 (19%)	7 (23%)	4 (50%)	33 (66%)
Ipsilateral PCA (P1 direction)	Correct	12 (75%)	22 (73%)	7 (88%)	42 (84%)
	Reversed	0 (0%)	0 (0%)	0 (0%)	1 (2%)
	Invisible	4 (25%)	8 (27%)	1 (12%)	7 (14%)
Ipsilateral PCoA	Anterior to posterior	1 (6%)	0 (0%)	0 (0%)	2 (4%)
	Posterior to anterior	2 (13%)	7 (23%)	2 (25%)	10 (20%)
	Invisible	13 (81%)	23 (77%)	6 (75%)	38 (76%)
Ipsilateral ophthalmic artery	Correct	7 (44%)	13 (43%)	3 (38%)	36 (72%)
	Reversed	6 (37%)	16 (53%)	4 (50%)	14 (28%)
	Invisible	3 (19%)	1 (3%)	1 (12%)	0 (0%)
ACoA	Right to left	4 (25%)	2 (7%)	2 (25%)	8 (16%)
	Left to right	1 (6%)	5 (17%)	1 (12%)	9 (18%)
	Balanced	2 (13%)	1 (3%)	0 (0%)	1 (2%)
	Invisible	9 (57%)	22 (73%)	5 (62%)	32 (64%)
Contralateral bone window adequate		16	36	7	50
Contralateral ACA (A1 direction)	Correct	12 (75%)	22 (61%)	7 (100%)	22 (44%)
	Reversed	0 (0%)	0 (0%)	0 (0%)	11 (22%)
	Invisible	4 (25%)	14 (39%)	0 (0%)	17 (34%)
Contralateral MCA	Abnormal	3 (19%)	8 (22%)	1 (14%)	13 (26%)
	Normal	13 (81%)	28 (78%)	6 (86%)	37 (74%)
Contralateral PCA (P1 direction)	Correct	11 (69%)	24 (67%)	6 (86%)	41 (82%)
	Reversed	0 (0%)	0 (0%)	0 (0%)	1 (2%)
	Invisible	5 (31%)	12 (33%)	1 (14%)	8 (16%)
Contralateral PCoA	Anterior to posterior	2 (13%)	1 (3%)	0 (0%)	5 (10%)
	Posterior to anterior	0 (0%)	2 (6%)	1 (14%)	6 (12%)
	Invisible	14 (87%)	33 (92%)	6 (86%)	39 (78%)
Contralateral ophthalmic artery	Correct	12 (75%)	33 (92%)	7 (100%)	40 (80%)
	Reversed	1 (6%)	2 (6%)	0 (0%)	9 (18%)
	Invisible	3 (19%)	1 (3%)	0 (0%)	1 (2%)

five occlusions were identified in patients with midline brain lesions or bilateral lesions.

Most of the 7% who did not have carotid imaging had had severe strokes and did not survive or were too ill to move for imaging. As expected, ipsilateral ICA occlusion was most common in patients with cortical and eye events and in those with more severe symptoms (fig 1).

There was a history of prior TIA or stroke in 7/22 TACIs (32%), 35/70 (50%) PACIs, and 8/14 (57%) cortical TIAs, but the difference was not significant (χ^2 $p = 0.33$)

Extracranial disease

Among patients with cortical symptoms (TACI, PACI, and cortical TIA) and ipsilateral ICA occlusion there was no significant difference in the prevalence of contralateral ICA disease (χ^2 for trend $p = 0.4$), ipsilateral external carotid (ECA) disease (χ^2 for trend $p = 0.6$), contralateral ECA disease (χ^2 for trend $p = 0.8$), or contralateral or ipsilateral vertebral abnormalities between the three groups (table 1). We repeated the analyses having excluded patients with previous stroke (that is, those whose ICA occlusion may have been symptomatic at some time in the past) but these data did not change the results (data available on request).

Collateral flow patterns of intracranial vessels

We looked for trends in collateral flow patterns (table 2) across patients with cortical symptoms (TACI, PACI, and cortical TIA). There were no trends in the proportions of patients with abnormal flow in the intracranial or ophthalmic artery circulation across the three groups with cortical symptoms. The only hint of a difference was that the ipsilateral MCA flow was more often reduced among the TACI and PACI than the cortical TIA patients, as one would expect soon after stroke, consistent with an MCA occlusion rather than indicating collateral flow. Note that the commonest finding was for potential collateral channels, for example the anterior or posterior communicating arteries, to be ''invisible'' but as functioning collateral arteries are usually large and readily visible, their invisibility indicates that these arteries were unlikely to be functioning as significant collaterals. Furthermore, although we have not performed formal statistical analysis due to the small numbers, there is no hint of any trend in potential collateral pathways across the three groups.

When we included the strokes and cortical TIAs with no brain imaging in the analyses, the results were very similar (full results available on request).

DISCUSSION

This large study of 2450 patients presenting with new neurological symptoms (ranging from transient symptoms to major disabling stroke) found that in those with ipsilateral ICA occlusion, there was no association between adequacy of potential collateral pathways and the severity of stroke symptoms. Although there is an extensive literature on ICA occlusion, few studies have investigated whether collaterals determine the severity and type of symptoms at the time of ICA occlusion, and most of these were either small and/or recruited patients with TIA or minor strokes.[2–5] The strength of our study was that we prospectively studied a large cohort of patients presenting to a broad based hospital stroke service, including a substantial number of patients with severe as well as mild strokes, TIAs, and retinal symptoms. Almost all underwent carotid imaging, and of those with ipsilateral ICA occlusion, most had TCD performed, resulting in a complete data set in the majority of patients.

There were some limitations to our study. Our stroke registry did not include asymptomatic people with an ICA occlusion (who might be expected to have the best collateral flow if our original hypothesis was correct)—the registry only recorded patients with symptoms. Also, we could not reliably distinguish ICA occlusion occurring at the time of the patients' presenting symptoms from those which may have occurred some time previously. However, even if the occlusion were longstanding, one might expect the severity of the presenting symptoms to relate to the adequacy of collaterals and therefore still have expected to observe a relationship between flow in collaterals and severity of symptoms. The group most likely to miss having carotid and transcranial Doppler studies (7% of 2397 patients) were the TACIs or POCIs who were more likely to die or be considered too ill for imaging. However, because we found no association between potential sources of intracranial collateral flow and the different patient groups, the exclusion of these few severe strokes probably did not influence our results. We used ultrasound rather than other imaging techniques because it is non-invasive, quick to perform, far more accessible than any other form of carotid imaging, and tolerated by the majority of patients, even those who are very ill. However, the intracranial vessels may be inaccessible in a substantial number of patients, and pathology in the intracranial internal carotid artery and basilar artery may be insufficiently evaluated by TCD.[18] The accuracy of duplex Doppler compared with angiography is high for carotid disease,[19] so even if we misclassified a few patients with severe ICA stenosis as ICA occlusion, this would not have affected the overall results. We did not examine cerebral perfusion patterns with PET or perfusion MR as it would not have been practical to perform these in such a large group of patients (including severe strokes) and would have restricted and biased our recruitment.

Therefore we still do not know why some patients with ICA occlusion develop severe stroke symptoms and others remain asymptomatic. The underlying cause of ICA occlusion (that is, cardioembolic or thrombus on atheroma) may influence the clinical effects of ICA occlusion by affecting the rate at which collateral vessels may develop.[20] Old cannot be distinguished from new ICA occlusions reliably on Doppler imaging, but the few postmortem studies of patients dying from ischaemic stroke show that the aetiology is generally fresh thrombus on pre-existing atheroma[20 21] and sudden embolic occlusion in the neck of a previously normal ICA is unusual. There are some data to support the notion that prior stroke or TIA may protect against the effects of sudden ICA occlusion by ''ischaemic pre-conditioning'',[22 23] and some that do not.[24] Our data provide no conclusive evidence either way. However, if prior TIA and stroke are protective, this could relate to use of antiplatelet drugs rather than changes in cerebrovascular haemodynamics, because patients with previous TIA or minor stroke would be more likely to be taking aspirin at the time of their index stroke.

Further work is required to determine what causes some ICA occlusions to cause severe strokes, but our data suggest that it does not seem to be a simple ''plumbing'' problem. It might be helpful to develop a technique for distinguishing old from new occlusions. Comparison of symptoms in presumed atherosclerotic occlusion (progressive occlusion, with time to develop collaterals) with presumed cardioembolic occlusion might help to determine whether the collateral vessels are important in determining the clinical effects of occlusion.

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Ethical approval (from Lothian Research Ethics Committee) was obtained for the study.

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